



NTP
National Toxicology Program

Triclosan Concept Review

Paul C. Howard, Ph.D.

National Center for Toxicological Research,
U.S. Food & Drug Administration

NTP Board of Scientific Counselors Meeting

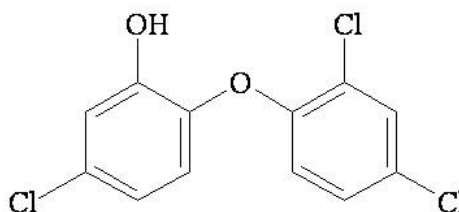
November 20-21, 2008





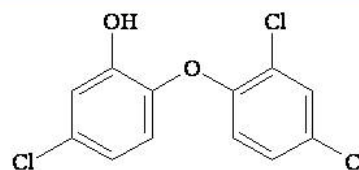
Nomination background

- Triclosan is a bacteriostatic & bacteriocidal chemical that is used in a wide variety of personal care products and industrial applications
- Triclosan was nominated by
(a) private individual, and
(b) FDA to the NTP
for dermal carcinogenicity testing due to:
 - High level of human topical exposure
 - Demonstrated transport through mucosal and skin tissues
 - Lack of dermal carcinogenicity data





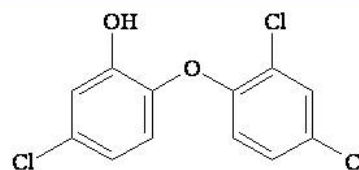
Human Exposure



- Included in many Personal Care Products
 - Included as bacteriostatic compound in
 - Antibacterial liquid soaps (hand-, body-, facial-washes; dish detergent)
 - Personal hygiene (deodorants, feminine products, anti-acne)
 - Dentifrices (toothpaste, 0.3%) and oral rinses
 - Kitchen appliances (utensils, cutting boards, surface wipes)
 - Other (children toys, mop heads, keyboards, blankets, paint, air filters ...)
- Use as Industrial Bactericide
 - Some commercial use in hospitals as pre-operative cleanser and as sanitizer to control bacteria (e.g. MRSA)



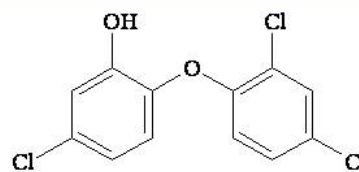
Human Exposure



- Evidence of Human Exposure
 - Presence in human serum and urine (mothers)
 - Present in serum regardless of triclosan use
 - Present in random urine samples (NHANES; 2 - 3,790 ng/mL)
 - Presence in human milk
 - Human milk, US; highest samples average 1.7 µg/g lipid (36 ng/g whole milk)
 - Human milk, Sweden, mothers using triclosan products (0.02-0.95 ng/g milk)
 - Average daily consumption in infants calculated at ~ 74 µg/kg/day
 - Environmental presence
 - Included in top 7 wastewater contaminants
 - Present in lakes and streams across world



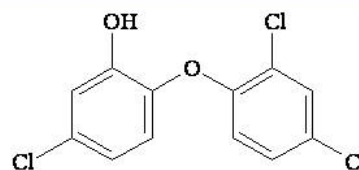
Human Exposure



- Humans
 - Absorbed through
 - Human oral and gastrointestinal mucosa (swallowing; toothpaste or mouth rinse; ppb levels in blood)
 - Human skin (6% penetration; 2-9% by urinary output)
- Animals
 - Absorption through skin, and gastrointestinal system
 - Plasma half-life 11-14 hrs



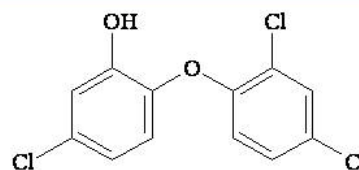
Mechanism of Action of Triclosan



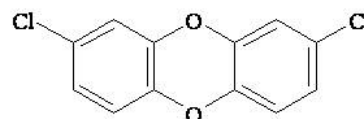
- Enzyme Inhibition
 - Inhibits bacterial Type II fatty acid synthase enoyl-reductase (Fab-I)
- Membrane interruption
 - Intercalation into membrane reducing viability
- Microbial resistance
 - Induction of Fab-I
 - Bacterial expression of mutated Fab-I with reduced triclosan binding
 - Drug efflux pumps



Triclosan Metabolism/Decomposition

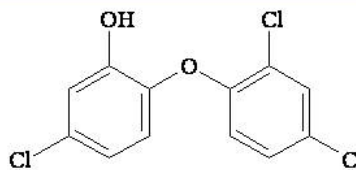


- Phase-I metabolism
 - Limited metabolism through hydroxylation and ether cleavage; primarily excreted without phase I metabolism
 - Induces cytochrome P450s (2B and 3A)
 - Inhibits uroporphyrinogen III synthetase
- Phase-II metabolism
 - Glucuronidation and sulfation at the ring hydroxyl group
- Combustion of triclosan
 - Textiles + triclosan at 600°C converted to 2,7- or 2,8-dichlorodibenzo-*p*-dioxin
 - Hypochlorite + combustion results in tri- and tetra- chlorodibenzo-*p*-dioxins
- Photodecomposition of triclosan
 - Photodehalogenation; photo-cleavage to phenols; photo-induced ring closure to dichlorodibenzo-*p*-dioxins





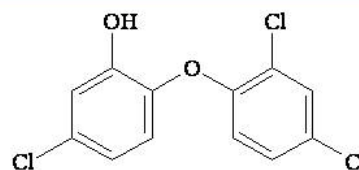
Triclosan Toxicity



- Mutagenicity Assays
 - Triclosan is not mutagenic
- Acute oral toxicity
 - Triclosan has very low acute toxicity
- Subchronic oral toxicity
 - NOAEL:
 - rats, 125 mg/kg & 150 mg/kg;
 - rabbits, gavage at 30 mg/kg, diet at 125 mg/kg;
 - dogs, capsule, 25-100 mg/kg



Triclosan Toxicity

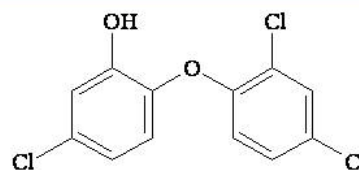


- Chronic oral toxicity/carcinogenicity
 - Baboons, 52 week oral dose, NOAEL of 30 mg/kg/day (*diarrhea, GI irritation*)
 - Rats, chronic studies submitted to FDA; EPA RED* NOAEL at 52 mg/kg/day (*non-neoplastic changes*)
 - Mouse, EPA RED NOAEL at 30 mg/kg/day (*liver adenoma/carcinoma, male and female*)
 - Hamster, EPA RED NOAEL at 75 mg/kg/day (*body weight, mortality, nephropathy, stomach and testes histopathology*)

*EPA RED; EPA Reregistration Eligibility Decision document, 29 Aug 2008



Triclosan Toxicity

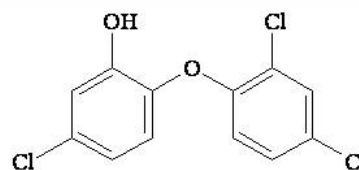


- Dermal toxicity studies.
 - Rat; 14 day study; EPA RED NOAEL of 3 mg/kg/day (*dermal irritation*)
 - Mouse; 14 day study; EPA RED NOAEL of <1.5 mg/kg/day (*dermal lesions, liver hypertrophy*)
 - Rats; 13 week study; NOAEL at 40 mg/kg (*dermal irritation in the dose groups; erythema, edema, desquamation, eschar formation; sebaceous gland hyperplasia, inflammation, focal necrosis on skin*); EPA RED agreement.
 - Not a dermal sensitizer in animals or humans.
 - No acceptable dermal carcinogenicity studies to date (FDA or EPA).

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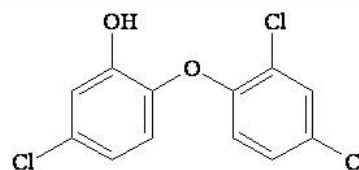
Triclosan Toxicity



- Reproductive and developmental toxicity
 - Rat; GD 6-15; NOAEL maternal 100 mg/kg/day, developmental >300 mg/kg/day
 - Rabbit; GD 6-18; NOAEL maternal 50 mg/kg/day, developmental >150 mg/kg/day
 - Mice; GD 6-15; NOAEL maternal 25 mg/kg/day, developmental 25 mg/kg/day
 - Rats; F₀-F₁; NOAEL parental 50 mg/kg/day, reproductive 50 mg/kg/day
- Aquatic toxicity
 - Weakly estrogenic in Japanese Medaka
 - Estrogen antagonist in frogs (*i.p.*) but lower doses reduced testosterone levels; binds to thyroid hormone receptor
 - Competes with estrogen receptor in MCF-7 cells; binds to rat androgen receptor



Key Issues

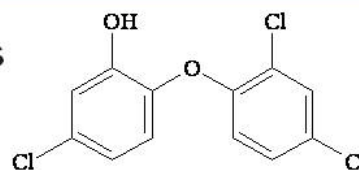


- Triclosan is applied to and absorbed through skin:
 - Triclosan is being applied to skin at significant rates as antibacterial compound
 - Triclosan is absorbed through the skin; suggesting that a gradient exists in the skin basal cells
- Lack of dermal carcinogenicity:
 - No published skin carcinogenicity studies
 - FDA has identified lack of skin carcinogenesis as primary gap in understanding triclosan risk (proper classification of triclosan)



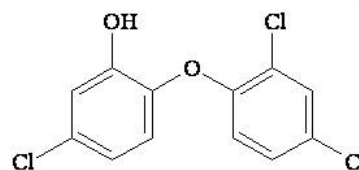
Proposed Approach to meet data needs

- The overall goal of the studies is to determine the dermal carcinogenic potential of triclosan
- Key data needs
 - Dermal carcinogenesis of topically applied triclosan
 - Determine if dichlorodibenzo-*p*-dioxins are formed *in vivo*
- Specific project components
 - Determine the pharmacokinetics of triclosan in mice following dermal application
 - Determine the dermal toxicity of triclosan (repeated dose) to establish dose range
 - Conduct the carcinogenesis study with widest possible dose range
 - Quantify photodecomposition of triclosan on skin:
 - i*, formation of phenols or chlorodibenzo-*p*-dioxins;
 - ii*, establish need for phototoxicity or photocarcinogenesis studies

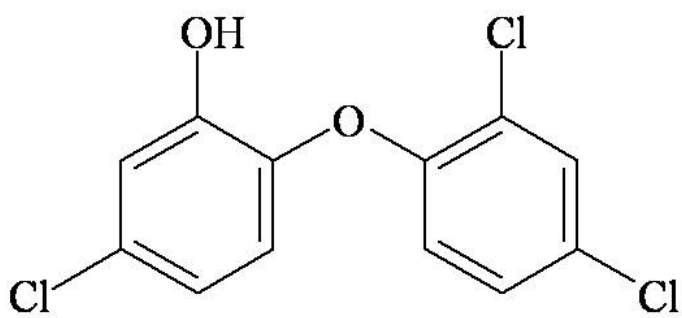




Benefit/Outcome

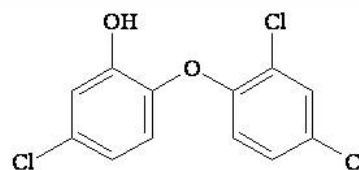


- Since 1978 triclosan categorized as Category III product (insufficient safety information); primarily due to insufficient dermal carcinogenicity data.
- FDA requests dermal carcinogenicity study due to:
 - High volume of dermal exposure to triclosan
 - Significant level of exposure from various products in all age groups for possibly life
 - Lack of published data on the dermal carcinogenicity with long term use.
- Dermal carcinogenicity data from studies will allow proper analysis of risk of triclosan, and subsequent proper classification.





Ciba Response to nomination:



- FDA agreement on some issues raised by Ciba:
 - e.g. Adequacy of ADME data in literature.
 - e.g. Willingness to fill perceived datagaps.
- FDA disagreement on some issues raised by Ciba:
 - e.g. Use in household cleaning products (not authorized, but occurs).
 - e.g. Adequacy of submitted dermal studies.
- FDA concludes:
 - Adequate dermal carcinogenesis have not been conducted and are needed for human health risk analysis and proper classification of triclosan.